REMARKS

Claims 1-28, 30-31, 34-35, 38-39 and 41-52 have been canceled without prejudice. Claims 29, 32-33, 36-37 and 40 are currently pending. Claims 32 and 36 have been amended. No new matter has been added.

Written Description

The Examiner has rejected pending claims 32 and 36 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. First, the Examiner states that "approximately 50 psi" is not supported because the specification references 40 psi and 60 psi. Additionally, the Examiner argues "between 60°C and 70°C" lacks written support because spray drying temperatures mentioned in the specification are 60°C and 70°C. Next, the Examiner states "approximately 18 standard cubic feet per minute (scfm)" is not supported because the flow rate supported in the specification is 17.8 scfm. Finally, the Examiner states "Humidity and relative humidity, although similar, are not equivalent."

Applicants respectfully rebut the rejections, noting that the ranges specified are well represented by the points described. Because the origin and termination of the range are assayed, and there is no reason to believe there would be any change in activity over such a **narrow range**, one of ordinary skill in the art would expect reasonable activity "between 40 and 60 psi" as well as "between 60°C and 70°C." Applicants request the Examiner provide evidence why additional support would be required across a narrow range and why there would be variability when both "40 and 60 psi" and "60°C and 70°C" were extremely repeatable and consistent.

Without conceding patentability, and in order to advance prosecution Applicants have amended claims 32 and 36 to recite "relative humidity," "17.8" ft^3/minute cubic and "between 40 and 60 psi." However, as these have essentially the same meaning as the prior language, no change in scope is effected.

Invention Directed to Treatment Methods, not Formulations

Applicants have cancelled all formulation claims without prejudice. Thus, arguments pertaining to formulations are no longer relevant.

Kurachi Irrelevant

Applicants do not understand Examiner's reliance on Kurachi. The structure of F.IX *in vivo* is irrelevant because the *in vivo* environment is nothing like the claimed environment. The claims refer to **aerosolized** F.IX and the art teaches that the process of aerosolizing F.IX denatures it (Gupta[1]).

Formulations not Identical, Thus Recited Elements Still Missing

Examiner asserts that the observation of unknown properties of the Lechuga formulation are not novel. However, the formulations are **not** identical:

Lechuga	Closest Formulation Described in 10/820,656
37% F.IX, 3% NaCitrate, 60% Leucine	32.6% F.IX, 7.4 % NaCitrate, 60% Leucine
56% F.IX, 4% NaCitrate, 40% Trileucine	52.6% F.IX, 7.4 % NaCitrate, 40% Trileucine

None of the cited art teaches the recited properties of activity, monomeric form, sequestration, etc. and one cannot **assume** that the Lechuga F.IX has the requisite properties **because the formulations were not identical**. Therefore, the *prima facie* case of obviousness is not made.

Allegedly Inherent Elements Not "Necessarily Present"

Inherency cannot be based on what might **or might not** be present. *In re Oelrich,* 666 F.2d 578, 581-82 (CCPA 1981) ("To establish inherency, the extrinsic evidence 'must make clear

[1] Gupta, Pulmonary Delivery of Human Protein C and Factor IX Oxygen Transport to Tissue XVIII, Chapter 55, p. 429-435 (1997) ("in the process of being aerosolized human Factor IX is **50% denatured** at the air water interface.")(emphasis added).

that the missing descriptive matter is **necessarily present** in the thing described in the reference...Inherency, however, may not be established by probabilities or possibilities...") (emphasis added). Here, since the formulations are **not** identical, one cannot **assume** that the requisite properties were in fact present.

Obviousness Case not Properly Based on Unknown Inherency

Even if the formulations were identical (and they are not) it is not proper to make an obviousness case based on **unknown** inherent properties of the Lechuga formulation. *In re Rijckaert,* 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("That which may be inherent is not necessarily known. **Obviousness cannot be predicated on what is unknown**.") (citations omitted).

No Reasonable Expectation of Success Evidenced by Gupta

It is well known in the art that proteins are difficult to aerosolize while maintaining activity[2] and Gupta actually teaches that **F.IX was denatured** during nebulization (Gupta[3]). Therefore, there is **no** reasonable expectation of success, and the *prima facie* case of obviousness is not made.[4]

Unexpected Results Found in Sequestration

Even if the *prima facie* case were made, Applicants provide competent evidence of unexpected results in the sequestration effect (see Application, Fig. 8 showing IV profile with

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[2] *See e.g.,* US5457044 ("aerosolization of aqueous solutions by nebulizer generates high shear forces which can **denature proteins**. Also, because of the surface-active nature of proteins, **surface fouling and foaming of the protein** can occur during nebulization of a protein solution.") (emphasis added).

[3] Gupta, Pulmonary Delivery of Human Protein C and Factor IX Oxygen Transport to Tissue XVIII, Chapter 55, p. 429-435 (1997) ("in the process of being aerosolized human Factor IX is **50% denatured** at the air water interface.")(emphasis added).

[4] Lechuga (WO0132144) fails to demonstrate the activity or form of spray dried F.IX—thus, Lechuga also fails to establish a reasonable expectation of success.

very high initial dose and rapid loss, as well as inhaled profile with dose remaining constant for at least 100 hrs).

The pharmacodynamic profile of inhaled F.IX is a significant (and surprising) improvement over the intravenous F.IX profile because it **avoids the large initial dose** and thus clotting difficulties due to the initial high dose of F.IX (see e.g., BeneFix package insert at http://www.wyeth.com/content/ShowLabeling.asp?id=92 noting that "use of factor IX complex concentrates has historically been associated with the development of thromboembolic complications")[5], and because the **dose remains constant** for at least 100 hours. Further, based on the surprisingly flat profile shown in Figure 8, one would expect that the F.IX would remain sufficiently high to prevent excess bleeding for at least one week. Thus, the clinical importance of this unexpected effect is also shown. This unexpected (and claimed) effect rebuts a *prima facie* case of obviousness.

Art and In Vivo Data Provide Competent Evidence

Applicants have shown **published statements** by Gupta and others in the field evidencing no reasonable expectation of success and ***in vivo* data** showing unexpected effects, thus establishing that the *prima facie* case is not made and/or rebutting the *prima facie* case. Competent rebuttal evidence taken as a whole should be weighed against the evidence supporting the *prima facie* case. *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). See also MPEP 716.01(d). In this case, there is **no** competent evidence for the opposing case. Thus, as a matter of law the unsupported rejections should be withdrawn.

Challenge for Competent Evidence

Applicants note that the Examiner has not provided any competent evidence to support his assertions, and Applicants hereby challenge all assertions as not properly Officially Noticed,

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[5] *See also*, Astrid van Hylckama Vlieg, *et al.,* **High levels of factor IX increase the risk of venous thrombosis,** Blood, 95(12):3678-3682 (2000) (emphasis added).

nor properly based upon common knowledge. Therefore, Applicants request that Examiner support his findings with adequate evidence pursuant to MPEP 2144.03.

CONCLUSION

Without additional evidence, Applicants have provided competent evidence of non-obviousness and request allowance of the currently presented claims.

The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 50-3420(reference 31176282-004001 MDB).

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Respectfully submitted,

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